AHRQ Comparative Effectiveness Review Surveillance Program

CER # 48:

Hematopoietic Stem-Cell Transplantation in the Pediatric Population

Original release date:

February 01, 2012

Surveillance Report:

October 29, 2012

Key Findings:

- KQ1, 2, 3, 4, 5 and 6 up to date
- Expert opinion: conclusions still valid
- There are no new significant safety concerns

Summary Decision:

This CER's priority for updating is **Low**

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None of the investigators has any affiliation or financial involvement that conflicts with material presented in this report

Acknowledgments

The authors gratefully acknowledge clinical content experts Drs Dunkel and Nemecek for their contributions to this project.

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Contents

Tables

Appendices

1. Introduction

The purpose of this mini-report was to apply the methodologies developed by the Ottawa and RAND EPCs to assess whether or not the CER No. 48 (Hematopoietic Stem-Cell Transplantation in the Pediatric Population),[1] is in need of updating. This CER was originally released in February, 2012. It was therefore due for a surveillance assessment in August, 2012.

This CER included 251 unique studies identified by using searches through August, 2011 and addressed six key questions to evaluate effectiveness and safety of hematopoietic stem-cell transplantation (HSCT) versus standard therapies or disease natural history in pediatric (age ≤21 years) patients with malignant solid tumors, inherited metabolic diseases, or autoimmune diseases. The key questions of the original CER were as follows:

1. For pediatric patients with malignant solid tumors, what is the comparative effectiveness of HSCT and conventional chemotherapy regarding overall survival, long-term consequences of HSCT, and quality of life?
2. For pediatric patients with malignant solid tumors, what are the comparative harms of HSCT and conventional chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?
3. For pediatric patients with inherited metabolic diseases, what is the comparative effectiveness of HSCT, enzyme-replacement therapy (ERT), and substrate reduction with iminosugars regarding overall survival, cure, long-term consequences of HSCT, and quality of life?
4. For pediatric patients with inherited metabolic diseases, what are the comparative harms of HSCT, ERT, and substrate reduction with iminosugars regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?
5. For pediatric patients with autoimmune diseases, what is the comparative effectiveness of HSCT, immunosuppressants, targeted biologic therapies, and low-dose chemotherapy regarding overall survival, cure, and remission?
6. For pediatric patients with autoimmune diseases, what are the comparative harms of HSCT, immunosuppressants, targeted biologic therapies, and lowdose chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?

The conclusion(s) for each key question are found in the executive summary of the CER report.[1]

2. Methods

We followed *a priori* formulated protocol to search and screen literature, extract relevant data, and assess signals for updating. The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The Food and Drug Administration (FDA), Health Canada, and Medicines and Healthcare Products Regulatory Agency (MHRA) safety surveillance alerts received from the Emergency Care Research Institute (ECRI) were examined for any relevant material for the present CER. The clinical expert opinion was also sought. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, safety surveillance alerts), a consensus-based conclusion was drawn whether or not any given conclusion warrants any updating (up to date, possibly out of date, or out of date). Based on this assessment, the CER was categorized into one of the three updating priority groups: high priority, medium priority, or low priority. Further details on the Ottawa EPC and RAND methods used for this project are found elsewhere.[2-4]

2.1 Literature Searches

The CER search strategies were reconstructed in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to September 25, 2012> and the Cochrane Central Register of Controlled Trials (CCRCT; search date August 27, 2012) as per the original search strategies appearing in the CER's Appendix A.[1] The syntax and vocabulary, which include both controlled subject headings (e.g., MeSH) and keywords, were applied according to the databases indicated in the appendix and in the search strategy section of the CER report. The MEDLINE search was limited to five general medical journals (Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine) and several specialty journals (Bone Marrow Transplantation, British journal of Haematology, Blood, Journal of clinical oncology, and Biology of Blood and Marrow Transplantation). Further details on the search strategies are provided in the Appendix A of this mini-report.

2.2 Study Selection

All identified bibliographic records were screened using a modified inclusion/exclusion criteria from one described in the original CER. This modification implied restricting the inclusion criteria to studies that provided direct comparison of the treatments. This decision was based on the fact that in the original CER almost all the conclusions were rated as low-strength or insufficient evidence because the evidence consisted of mostly uncontrolled single-arm studies and case reports. Studies with direct comparisons of treatment are necessary to increase this strength of evidence. Hence, for this surveillance assessment we included only studies with direct comparisons of treatments.

2.3 Expert Opinion

In total, 10 content experts were requested to provide their feedback in a pre-specified matrix table on whether or not the conclusions as outlined in the Executive Summary of the original CER were still valid.

2.4 Check for Qualitative and Quantitative Signals

All relevant reports eligible for inclusion in the CER were examined for the presence of qualitative and quantitative signals using the Ottawa EPC method (see more details in Appendix B). CERs with no meta-analysis were examined for qualitative signals only. For any given CER that included a meta-analysis, the assessment started with the identification of qualitative signal(s), and if no qualitative signal was found, this assessment extended to identify any quantitative signal(s). The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The definition and categories of updating signals are presented in Appendix B and publications.[2]

2.5 Compilation of Findings and Conclusions

All the information obtained during the updating process (i.e., data on qualitative/quantitative signals, the expert opinions, and safety surveillance alerts) was collated and summarized. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, and safety surveillance alerts) presented in a tabular form, a conclusion was drawn whether or not any conclusion(s) of the CER warrant(s) updating.
Conclusions were drawn based on four category scheme:

- Original conclusion is still **up to date** and this portion of CER does not need updating
- Original conclusion is **possibly out of date** and this portion of CER may need updating
- Original conclusion is **probably out of date** and this portion of CER may need updating
- Original conclusion is **out of date** and this portion of CER is in need of updating

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still up to date.

- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.

- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

Determination of priority groups (i.e., Low, Medium, and High) for updating any given CER was based on two criteria:

- How many conclusions of the CER are up to date, possibly out of date, or certainly out of date?
- How out of date are conclusions (e.g., consideration of magnitude/direction of changes in estimates, potential changes in practice or therapy preference, safety issue including withdrawn from the market drugs/black box warning, availability of a new treatment)

3. Results

3.1 Update Literature Searches and Study Selection

A total of 262 bibliographic records were identified (MEDLINE=255 and CCRCT =7). After de-duping, 255 records remained (MEDLINE=253 and CCRCT=2), from which 34 potentially eligible records were assessed for full text. None of the 34 studies was included in the update (all reports described single-arm case-series without a comparator).

3.2 Signals for Updating in Newly Identified Studies

3.2.1 Study overview

No new evidence

3.2.2 Qualitative signals

See also Table 1 (Summary Table), Appendix B, and Evidence Table (Appendix C)

Key questions #1-6
No new evidence

3.2.3 Quantitative signals

See also Table 1 (Summary Table), Appendix B, and Evidence Table (Appendix C)

Key questions #1-6
No new evidence

3.3 Safety surveillance alerts

None of the received safety surveillance alerts was relevant to the key questions of the given CER.

3.4Expert opinion

Two of the 10 contacted clinical experts (one technical expert panel member and one peer reviewer of the original CER) provided their response in the matrix table (Appendix D). Overall, both experts agreed with the conclusions and were not aware of evidence that would invalidate the four CER conclusions.

4. Conclusion

Summary results and conclusions according to the information collated from different sources (updating signals from studies identified through the update search, safety surveillance alerts, and expert opinion) are provided in Table 1 (Summary Table). Based on the assessments, this CER is categorized in **Low** priority group for updating.

Key Question # 1

Signals from studies identified through update search: No new evidence. **No Signal.**
Experts: Still valid
Safety surveillance alerts: No
Conclusion: **Up to date**

Key Question # 2
Signals from studies identified through update search: No new evidence. **No Signal.**
Experts: Still valid
Safety surveillance alerts: No
Conclusion: **Up to date**

Key Question # 3
Signals from studies identified through update search: No new evidence. **No Signal.**
Experts: Still valid
Safety surveillance alerts: No
Conclusion: **Up to date**

Key Question # 4
Signals from studies identified through update search: No new evidence. **No Signal.**
Experts: Still valid
Safety surveillance alerts: No
Conclusion: **Up to date**

Key question # 5
Signals from studies identified through update search: No new evidence. **No Signal.**
Experts: Still valid
Safety surveillance alerts: No
Conclusion: **Up to date**

Key question # 6
Signals from studies identified through update search: No new evidence. **No Signal.**
Experts: Still valid
Safety surveillance alerts: No
Conclusion: **Up to date**

Table 1. Summary Table

Conclusions from CER's Executive Summary	Update literature search results	Signals for updating		Safety surveillance alerts	Expert opinion	Conclusion on validity of CER conclusion(s)
		Qualitative	Quantitative			
Key Question 1: For pediatric patients with malignant solid tumors, what is the comparative effectiveness of HSCT and conventional chemotherapy regarding overall survival, long-term consequences of HSCT, and quality of life?						
Low-strength evidence on overall survival suggests a benefit with single HSCT compared with conventional therapy for *high-risk recurrent or progressive anaplastic astrocytoma*. Moderate-strength evidence on overall survival suggests no benefit with single HSCT compared with conventional therapy for *metastatic rhabdomyosarcoma*. Low-strength evidence on overall survival suggests no benefit with single HSCT compared with conventional therapy for *extraocular retinoblastoma* with CNS (central nervous system) involvement, *high-risk Ewing's sarcoma family of tumors*, and *high-risk relapsed Wilm's tumor*. The body of evidence on overall survival with tandem HSCT compared with single HSCT is insufficient to draw conclusions for *high-risk Ewing's sarcoma family of tumors, neuroblastoma, CNS embryonal tumors, and pediatric germ cell tumors*. The body of evidence on overall survival with single HSCT compared with conventional therapy is insufficient to draw conclusions for *CNS embryonal tumors, high-risk rhabdomyosarcoma of mixed stages, congenital alveolar rhabdomyosarcoma, cranial parameningeal rhabdomyosarcoma with metastasis, allogeneic transplantation for metastatic rhabdomyosarcoma, extraocular retinoblastoma with no CNS involvement, trilateral retinoblastoma, and* six types of glial tumors *(newly diagnosed anaplastic astrocytoma, newly diagnosed glioblastoma multiforme, anaplastic*	No new evidence	NA	NA	None	One expert may not agree that "low-strength evidence on overall survival suggests a benefit with single HSCT compared with conventional therapy for *high-risk recurrent or progressive anaplastic astrocytoma*." The expert believes that very only few pediatric neuro-oncologists use HSCT for *high-risk recurrent or progressive anaplastic astrocytoma* However, the expert believes that HSCT is beneficial for	Up to date

ependymoma, choroid plexus carcinoma, recurrent/progressive glioblastoma multiforme, and *nonanaplastic, mixed,* or *unspecified ependymoma*).					extra-ocular retinoblastoma not involving the CNS (stage 4a RB) and trilateral retinoblastoma. No references were provided The second expert agreed with the conclusion	
Key question 2: For pediatric patients with malignant solid tumors, what are the comparative harms of HSCT and conventional chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?						
Low-strength evidence on overall survival suggests harm due to higher treatment-related mortality with single HSCT compared with conventional chemotherapy for *nonanaplastic mixed* or *unspecified ependymoma*.	No new evidence	NA	NA	None	One expert agreed with the conclusion; the other did not know the answer	Up to date
Key question 3: For pediatric patients with inherited metabolic diseases, what is the comparative effectiveness of HSCT, enzyme-replacement therapy (ERT), and substrate reduction with iminosugars regarding overall survival, cure, long-term consequences of HSCT, and quality of life?						
<u>Rapidly Progressive Diseases</u> High-strength evidence on overall survival suggests a benefit with single HSCT compared with conventional management for *Wolman's disease*. Low-strength evidence on overall survival suggests no benefit with single HSCT compared with symptom management or disease natural history for *Niemann-Pick Type A*. The body of evidence on overall survival with single HSCT compared with symptom management is insufficient to draw conclusions for *mucolipidosis II (I-cell disease), Gaucher disease type II, cystinosis, and infantile*	No new evidence	NA	NA	None	Both experts did not know the answer One expert did not know the answer; the other agreed with the conclusions	Up to date

free sialic acid disease. **<u>Slowly Progressive Diseases</u>** Low-strength evidence on neurodevelopmental outcomes suggests a benefit with single HSCT compared with enzyme replacement therapy for *attenuated and severe forms of MPS* (mucopolysaccharidosis) *II* (Hunter's disease). Low-strength evidence on neurocognitive outcomes suggests a benefit with single HSCT compared with enzyme replacement therapy for *attenuated form of MPS II* (Hunter's disease). Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with enzyme replacement therapy for *Gaucher disease type III*. Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with enzyme replacement therapy for the *severe form of MPS II* (Hunter's disease). Low-strength evidence on neurocognitive or neurodevelopmental outcomes suggests no benefit with single HSCT compared with symptom management, substrate reduction therapy, or disease natural history for *MPS III* (Sanfilippo). The body of evidence on neurocognitive or neurodevelopmental outcomes with single HSCT compared with symptom management and/or disease natural history is insufficient to draw conclusions for *Niemann-Pick type C, MPS IV* (Morquio syndrome), *aspartylglucosaminuria, Fabry's disease, β-mannosidosis, mucolipidosis III, mucolipidosis IV, glycogen storage disease type II* (Pompe disease), *Salla disease,* and *adrenomyeloneuropathy.* **<u>Both Rapidly and Slowly Progressive Diseases</u>**					See above	

High-strength evidence on number of subcutaneous nodules and number of joints with limited range of motion suggests a benefit with single HSCT compared with symptom management or disease natural history for *Farber's disease type 2/3*. Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with symptom management or disease natural history for *infantile ceroid lipofuscinosis*. The body of evidence on overall survival and/or neurocognitive and neurodevelopmental outcomes with single HSCT compared with symptom management and/or disease natural history is insufficient to draw conclusions for *galactosialidosis* (type unspecified), *Sandhoff disease* (type unspecified), *Farber's disease type I, infantile GM1 gangliosidosis, juvenile GM1 gangliosidosis, infantile Tay-Sachs, juvenile Tay-Sachs*, and *juvenile ceroid lipofuscinosis.*						
Key question 4: For pediatric patients with inherited metabolic diseases, what are the comparative harms of HSCT, ERT, and substrate reduction with iminosugars regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?						
See Key Question 3	-	-	-	-	-	-
Key question 5: For pediatric patients with autoimmune diseases, what is the comparative effectiveness of HSCT, immunosuppressants, targeted biologic therapies, and low-dose chemotherapy regarding overall survival, cure, and remission?						
The overall body of evidence is insufficient to draw conclusions about the comparative benefits (e.g., increased overall survival) or harms (e.g., treatment-related mortality, secondary malignancies) of single autologous or allogeneic HSCT versus conventional therapy or disease natural history in patients with *newly diagnosed type 1 juvenile diabetes mellitus* or those with *severe, refractory, poor-prognosis autoimmune diseases*, including *systemic lupus erythematosus, juvenile idiopathic arthritis, systemic sclerosis, malignant multiple sclerosis, Crohn's disease, myasthenia gravis, overlap syndrome, diffuse cutaneous cutis, Evans syndrome, autoimmune hemolytic anemia*, and *autoimmune cytopenia*.	No new evidence	NA	NA	None	One expert did not know the answer; the other expert agrees with the conclusions	Up to date

Although the overall body of evidence is insufficient to come to conclusions about the relative balance of benefits (e.g., increased overall survival) or harms (e.g., treatment related mortality, secondary malignancies), moderate-strength evidence suggests that extended periods of drug-free clinical remission can be achieved in some cases with single autologous HSCT for patients with *newly diagnosed type I juvenile diabetes* and patients with *severe refractory juvenile idiopathic arthritis, systemic lupus erythematosus, systemic sclerosis,* and *Crohn's disease*.						
Key question 6: For pediatric patients with autoimmune diseases, what are the comparative harms of HSCT, immunosuppressants, targeted biologic therapies, and low dose chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?						
See Key Question 5	-	-	-	-	-	-
CER=comparative effectiveness review; HSCT= hematopoietic stem-cell transplantation; NA=not applicable; CNS=central nervous system; ERT=enzyme replacement therapy						

References

1. Ratko TA, Belinson SE, Brown HM et al. Hematopoietic Stem-Cell Transplantation in the Pediatric Population. 12-EHC018-EF. Agency for Healthcare Research and Quality (US); 2012.

2. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 2007 Aug 21;147(4):224-33. [PMID: PM:17638714]

3. Shekelle PG, Newberry SJ, Wu H et al. Identifying Signals for Updating Systematic Reviews: A comparison of two methods [Internet]. 11-EHC042-EF. Agency for Healthcare Research and Quality (US); 2011.

4. Shekelle P, Newberry S, Maglione M et al. Assessment of the Need to Update Comparative Effectiveness Reviews: Report of an Initial Rapid Program Assessment (2005-2009) [Internet]. Agency for Healthcare Research and Quality (US); 2009.

Appendix A: Search Methodology

All MEDLINE searches were limited to the following journals:

General biomedical – Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine

Specialty journals – Bone Marrow Transplantation, British journal of Haematology, Blood, Journal of clinical oncology, and Biology of Blood and Marrow Transplantation

Database: Ovid MEDLINE(R)

Time period covered: February 18, 2011 to September 25, 2012

1 exp Bone Marrow Transplantation/ (40112)
2 exp Stem Cell Transplantation/ (46191)
3 exp Peripheral Blood Stem Cell Transplantation/ (2569)
4 exp Cord Blood Stem Cell Transplantation/ (1833)
5 exp Hematopoietic Stem Cell Transplantation/ (24655)
6 ("stem cell*" or "bone marrow").mp. (337789)
7 or/1-6 (337789)
8 exp Sarcoma, Ewing/ (5356)
9 exp Wilms Tumor/ (7762)
10 exp Rhabdomyosarcoma/ (8763)
11 exp Retinoblastoma/ (5760)
12 exp Medulloblastoma/ (5278)
13 exp Neuroectodermal Tumors, Primitive/ (30900)
14 exp Astrocytoma/ (23637)
15 exp Mucopolysaccharidoses/ (5112)
16 exp Sphingolipidoses/ (11200)
17 exp Lysosomal Storage Diseases/ (20064)
18 exp Glycogen Storage Disease/ (4873)
19 exp Niemann-Pick Diseases/ (1827)
20 exp Adrenoleukodystrophy/ (1413)
21 exp Arthritis, Juvenile Rheumatoid/ (7932)
22 exp Lupus Erythematosus, Systemic/ (46170)
23 exp Scleroderma, Systemic/ (15656)
24 exp Crohn Disease/ (27861)
25 exp Autoimmune Diseases/ (359445)
26 ("Ewing's Sarcoma" or "Wilms Tumor" or Rhabdomyosarcoma* or Retinoblastoma* or Medulloblastoma* or PNET or "Primitive Neuroectodermal Tumor*" or Astrocytoma* or Mucopolysaccharidos* or Sphingolipidos* or "Lysosomal Storage Disease*").mp. (73530)
27 ("Glycogen Storage Disease*" or "Niemann-Pick Disease*" or Adrenoleukodystrophy or "Juvenile Rheumatoid Arthritis" or "Systemic Lupus Erythematosus" or SLE or Scleroderma or "Crohn Disease" or "Crohn's disease" or "Autoimmune Disease*").mp. (161524)

28 ("Fabry Disease" or "Fabry's disease" or "Farber Lipogranulomatosis" or Gangliosidos*).mp. (4310)
29 ("Sandhoff Disease" or "sandhoff's disease" or "Gaucher Disease" or "gaucher's disease" or "Niemann-Pick Disease*" or "Tay-Sachs Disease").mp. (7731)
30 (Aspartylglucosaminuria or "beta-Mannosidosis" or Mucolipidos* or "Wolman Disease" or "Ceroid Lipofuscinos*" or "Ceroid-Lipofuscinos*" or galactosialidosis or Cystinosis).mp. (4649)
31 ("Sialic Acid Storage Disease" or "salla disease" or "peroxisomal storage disorder*" or adrenomyeloneuropath* or "immune cytopenia*").mp. (612)
32 exp "Neoplasms, Germ Cell and Embryonal"/ (256042)
33 ("germ cell tumor*" or "germ cell cancer" or "germ cell tumour*").mp. (8444)
34 exp Anemia, Diamond-Blackfan/ (259)
35 (("Diamond-Blackfan" or "Diamond Blackfan") and (anemia or syndrome)).mp. (566)
36 exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/ (19651)
37 exp Leukemia, Myeloid, Acute/ (40396)
38 ("acute lymphoblastic leukemia" or "acute myeloid leukemia").mp. (29311)
39 exp Lymphoma, Non-Hodgkin/ (77774)
40 "non-Hodgkin* lymphoma*".mp. (27214)
41 exp Hodgkin Disease/ (29736)
42 "hodgkin lymphoma".mp. (8084)
43 exp Leukemia, Myelomonocytic, Juvenile/ (120)
44 "juvenile myelomonocytic leukemia".mp. (314)
45 exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/ (14574)
46 "chronic myelogenous leukemia".mp. (6570)
47 exp Myelodysplastic-Myeloproliferative Diseases/ (1412)
48 "myelodysplastic disease*".mp. (34)
49 exp Neuroblastoma/ (23570)
50 neuroblastoma*.mp. (31825)
51 exp Leukodystrophy, Globoid Cell/ (774)
52 "globoid leukodystrophy".mp. (30)
53 exp Leukodystrophy, Metachromatic/ (1047)
54 "metachromatic leukodystrophy".mp. (965)
55 exp Fucosidosis/ (130)
56 fucosidosis.mp. (286)
57 exp alpha-Mannosidosis/ (227)
58 ("alpha-mannosidosis" or "alpha-mannosidoses").mp. (276)
59 exp Peroxisomal Disorders/ (2981)
60 ("peroxisomal storage disorder*" or adrenoleukodystroph*).mp. (1877)
61 exp Osteopetrosis/ (2282)
62 osteopetrosis.mp. (2788)
63 "bone marrow failure".mp. (1820)
64 exp Fanconi Anemia/ (2406)
65 "Fanconi* anemia".mp. (3310)
66 exp Dyskeratosis Congenita/ (379)
67 ("dyskeratosis congenita" or "Shwachman-Diamond" or "Diamond-Blackfan" or "Diamond Blackfan").mp. (1436)
68 exp Ependymoma/ (4195)

69 ependymoma*.mp. (5383)
70 exp Glioma/ (55403)
71 glioma.mp. (35887)
72 exp Choroid Plexus Neoplasms/ (617)
73 ("choroid plexus" and (tumor or tumour or tumors or tumours or neoplasm*)).mp. (1944)
74 medulloepithelioma*.mp. (252)
75 (supratentorial and (PNET or "primitive neuroectodermal")).mp. (302)
76 (pineoblastoma* or "cerebral neuroblastoma*" or ganglioneuroblastoma* or ependymoblastoma* or "atypical teratoid/rhabdoid tumor*").mp. (1619)
77 exp Pinealoma/ (1491)
78 exp Rhabdoid Tumor/ and (atypical and teratoid*).mp. (249)
79 exp Astrocytoma/ (23637)
80 exp Oligodendroglioma/ (2983)
81 (astrocytoma* or oligodendroglioma* or "glioblastoma multiforme").mp. (23634)
82 exp Diabetes Mellitus, Type 1/ (57337)
83 (("type 1" and (diabetes or diabetic or DM)) or "juvenile diabetes").mp. (68063)
84 or/8-83 (963573)
85 7 and 84 (64223)
86 limit 85 to (english language and humans and "all child (0 to 18 years)") (15930)
87 lancet.jn. (122885)
88 jama.jn. (62783)
89 "annals of internal medicine".jn. (27600)
90 bmj.jn. (74392)
91 "new england journal of medicine".jn. (65985)
92 "biology of blood & marrow transplantation".jn. (2306)
93 bone marrow transplantation.jn. (9198)
94 "british journal of haematology".jn. (17940)
95 "journal of clinical oncology".jn. (18831)
96 blood.jn. (40522)
97 or/87-96 (442442)
98 86 and 97 (4289)
99 ("20110218" or "20110221" or "20110222" or "20110223" or "20110224" or "20110225" or "20110228" or 201103* or 201104* or 201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012*).ed. (1567877)
100 98 and 99 (255)

Database: Cochrane Central Register of Clinical Trials

Time period covered: January 01, 2011 to August 27, 2012

ID		
#1	MeSH descriptor Hematopoietic Stem Cell Transplantation explode all trees	841
#2	(pediatric or child or children or adolescence or adolescents):ti,ab,kw	117619
#3	(#1 AND #2)	319
#4	(#3), from 2011 to 2012	21

DSR - 3
DARE - 2
CENTRAL – 16 (reduced to 7 for selected journals)

Appendix B: Updating Signals

Qualitative signals*

Potentially invalidating change in evidence

This category of signals (A1-A3) specifies findings from a pivotal trial**, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of "opposing findings" – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

* Please, see Shojania et al. 2007[2] for further definitions and details

**A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

Appendix B: Updating Signals (Continued)

Quantitative signals (B1-B2)*

Change in statistical significance (B1)

Refers to a situation in which a statistically significant result in the original CER is now NOT statistically significant or vice versa- that is a previously non-significant result become statistically significant. For the 'borderline' changes in statistical significance, at least one of the reports (the original CER or new updated meta-analysis) must have a p-value outside the range of border line (0.04 to 0.06) to be considered as a quantitative signal for updating.

Change in effect size of at least 50% (B2)

Refers to a situation in which the new result indicates a relative change in effect size of at least 50%. For example, if relative risk reduction (RRR) new / RRR old <=0.5 or RRR new / RRR old >=1.5. Thus, if the original review has found RR=0.70 for mortality, this implies RRR of 0.3. If the updated meta-analytic result for mortality were 0.90, then the updated RRR would be 0.10, which is less than 50% of the previous RRR. In other words the reduction in the risk of death has moved from 30% to 10%. The same criterion applied for odds ratios (e.g., if previous OR=0.70 and updated result were OR=0.90, then the new reduction in odds of death (0.10) would be less 50% of the magnitude of the previous reduction in odds (0.30). For risk differences and weighted mean differences, we applied the criterion directly to the previous and updated results (e.g., RD new / RD old <=0.5 or RD new / RD old >=1.5).

* Please, see Shojania et al. 2007[2] for further definitions and details

Appendix C: Evidence Table

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcomes and findings
Key Question # 1: For pediatric patients with malignant solid tumors, what is the comparative effectiveness of HSCT and conventional chemotherapy regarding overall survival, long-term consequences of HSCT, and quality of life?					
No new evidence	NA	NA	NA	NA	NA
Key question # 2: For pediatric patients with malignant solid tumors, what are the comparative harms of HSCT and conventional chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?					
No new evidence	NA	NA	NA	NA	NA
Key question # 3: For pediatric patients with inherited metabolic diseases, what is the comparative effectiveness of HSCT, enzyme-replacement therapy (ERT), and substrate reduction with iminosugars regarding overall survival, cure, long-term consequences of HSCT, and quality of life?					
No new evidence	NA	NA	NA	NA	NA
Key question # 4: For pediatric patients with inherited metabolic diseases, what are the comparative harms of HSCT, ERT, and substrate reduction with iminosugars regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?					
No new evidence	NA	NA	NA	NA	NA
Key question # 5: For pediatric patients with autoimmune diseases, what is the comparative effectiveness of HSCT, immunosuppressants, targeted biologic therapies, and low-dose chemotherapy regarding overall survival, cure, and remission?					
No new evidence	NA	NA	NA	NA	NA
Key question # 6: For pediatric patients with autoimmune diseases, what are the comparative harms of HSCT, immunosuppressants, targeted biologic therapies, and low dose chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?					
No new evidence	NA	NA	NA	NA	NA
CER=comparative effectiveness review; RCT=randomized controlled trial; NA=not applicable; HSCT=hematopoietic stem-cell transplantation; ERT=enzyme replacement therapy					

Appendix D: Questionnaire Matrix

Comparative Effectiveness Review: Hematopoietic Stem-Cell Transplantation in the Pediatric Population

AHRQ Publication No. 12-EHC018-EF 2012

Access to full report: http://effectivehealthcare.ahrq.gov/ehc/products/148/945/CER48_Stem-Cell_executivesummary_20120131.pdf

Clinical expert name:

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question # 1: For pediatric patients with malignant solid tumors, what is the comparative effectiveness of HSCT and conventional chemotherapy regarding overall survival, long-term consequences of HSCT, and quality of life?			
Low-strength evidence on overall survival suggests a benefit with single HSCT compared with conventional therapy for *high-risk recurrent or progressive anaplastic astrocytoma*. Moderate-strength evidence on overall survival suggests no benefit with single HSCT compared with conventional therapy for *metastatic rhabdomyosarcoma*. Low-strength evidence on overall survival suggests no benefit with single HSCT compared with conventional therapy for *extraocular retinoblastoma with CNS* (central nervous system) *involvement, high-risk Ewing's sarcoma family of tumors*, and *high-risk relapsed Wilm's tumor*.			

The body of evidence on overall survival with tandem HSCT compared with single HSCT is insufficient to draw conclusions for *high-risk Ewing's sarcoma family of tumors, neuroblastoma, CNS embryonal tumors,* and *pediatric germ cell tumors*. The body of evidence on overall survival with single HSCT compared with conventional therapy is insufficient to draw conclusions for *CNS embryonal tumors, high-risk rhabdomyosarcoma of mixed stages, congenital alveolar rhabdomyosarcoma, cranial parameningeal rhabdomyosarcoma with metastasis, allogeneic transplantation for metastatic rhabdomyosarcoma, extraocular retinoblastoma with no CNS involvement, trilateral retinoblastoma,* and six types of glial tumors (*newly diagnosed anaplastic astrocytoma, newly diagnosed glioblastoma multiforme, anaplastic ependymoma, choroid plexus carcinoma, recurrent/progressive glioblastoma multiforme*, and *nonanaplastic, mixed, or unspecified ependymoma*).			
Key question # 2: For pediatric patients with malignant solid tumors, what are the comparative harms of HSCT and conventional chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?			
Low-strength evidence on overall survival suggests harm due to higher treatment-related mortality with single HSCT compared with conventional chemotherapy for *nonanaplastic mixed or unspecified ependymoma*.			
Key question # 3: For pediatric patients with inherited metabolic diseases, what is the comparative effectiveness of HSCT, enzyme-replacement therapy (ERT), and substrate reduction with iminosugars regarding overall survival, cure, long-term consequences of HSCT, and quality of life?			
<u>Rapidly progressive diseases</u> High-strength evidence on overall survival suggests a benefit with single HSCT compared with conventional management for *Wolman's disease*. Low-strength evidence on overall survival suggests no			

benefit with single HSCT compared with symptom management or disease natural history for *Niemann-Pick Type A.* The body of evidence on overall survival with single HSCT compared with symptom management is insufficient to draw conclusions for *mucolipidosis II* (I-cell disease), *Gaucher disease type II*, *cystinosis,* and *infantile free sialic acid disease*. **<u>Slowly progressive diseases</u>** Low-strength evidence on neurodevelopmental outcomes suggests a benefit with single HSCT compared with enzyme replacement therapy for *attenuated and severe forms of MPS* (mucopolysaccharidosis) *II* (Hunter's disease). Low-strength evidence on neurocognitive outcomes suggests a benefit with single HSCT compared with enzyme replacement therapy for *attenuated form of MPS II* (Hunter's disease). Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with enzyme replacement therapy for *Gaucher disease type III*. Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with enzyme replacement therapy for the *severe form of MPS II* (Hunter's disease). Low-strength evidence on neurocognitive or neurodevelopmental outcomes suggests no benefit with single HSCT compared with symptom management, substrate reduction therapy, or disease natural history			

for *MPS III* (Sanfilippo). The body of evidence on neurocognitive or neurodevelopmental outcomes with single HSCT compared with symptom management and/or disease natural history is insufficient to draw conclusions for *Niemann-Pick type C*, *MPS IV* (Morquio syndrome), *aspartylglucosaminuria*, *Fabry's disease*, *β-mannosidosis*, *mucolipidosis III*, *mucolipidosis IV*, *glycogen storage disease type II* (Pompe disease), *Salla disease*, and *adrenomyeloneuropathy*. **<u>Both rapid and slowly progressive diseases</u>** High-strength evidence on number of subcutaneous nodules and number of joints with limited range of motion suggests a benefit with single HSCT compared with symptom management or disease natural history for *Farber's disease type 2/3*. Low-strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared with symptom management or disease natural history for *infantile ceroid lipofuscinosis*. The body of evidence on overall survival and/or neurocognitive and neurodevelopmental outcomes with single HSCT compared with symptom management and/or disease natural history is insufficient to draw conclusions for *galactosialidosis* (type unspecified), *Sandhoff disease* (type unspecified), *Farber's disease type I*, *infantile GM1 gangliosidosis*, *juvenile GM1 gangliosidosis*, *infantile Tay-Sachs*, *juvenile Tay-Sachs*, and *juvenile ceroid lipofuscinosis*.			
Key question # 4: For pediatric patients with inherited metabolic diseases, what are the comparative harms of HSCT, ERT, and substrate reduction with iminosugars regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?			
See Key Question 3			

Key question # 5: For pediatric patients with autoimmune diseases, what is the comparative effectiveness of HSCT, immunosuppressants, targeted biologic therapies, and low-dose chemotherapy regarding overall survival, cure, and remission?			
The overall body of evidence is insufficient to draw conclusions about the comparative benefits (e.g., increased overall survival) or harms (e.g., treatment-related mortality, secondary malignancies) of single autologous or allogeneic HSCT versus conventional therapy or disease natural history in patients with *newly diagnosed type 1 juvenile diabetes mellitus* or those with severe, refractory, poor-prognosis autoimmune diseases, including *systemic lupus erythematosus*, *juvenile idiopathic arthritis*, *systemic sclerosis*, *malignant multiple sclerosis*, *Crohn's disease*, *myasthenia gravis*, *overlap syndrome*, *diffuse cutaneous cutis*, *Evans syndrome*, *autoimmune hemolytic anemia*, and *autoimmune cytopenia*. Although the overall body of evidence is insufficient to come to conclusions about the relative balance of benefits (e.g., increased overall survival) or harms (e.g., treatment related mortality, secondary malignancies), moderate-strength evidence suggests that extended periods of drug-free clinical remission can be achieved in some cases with single autologous HSCT for patients with *newly diagnosed type I juvenile diabetes* and patients with severe refractory *juvenile idiopathic arthritis*, *systemic lupus erythematosus*, *systemic sclerosis*, and *Crohn's disease*.			
Key question # 6: For pediatric patients with autoimmune diseases, what are the comparative harms of HSCT, immunosuppressants, targeted biologic therapies, and low dose chemotherapy regarding adverse effects of treatment, long-term consequences of HSCT, and impaired quality of life?			
See Key Question 5			
CER=comparative effectiveness review; HSCT=hematopoietic stem-cell transplantation; ERT=enzyme replacement therapy; CNS=central nervous system			